Increased hepatic glucose production and insulin resistance in subjects with non-alcoholic fatty liver disease is associated to increased plasma concentrations of glucogenic amino acids

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Fatty liver disease: Experimental and pathophysiology

Increased hepatic glucose production and insulin resistance in subjects with NAFLD is associated to increased plasma concentrations of glucogenic amino acids

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Background and Aims: The liver plays a central role in the regulation of glucose metabolism, being the major site of endogenous glucose production (EGP) during fasting and of glucose storage (as glycogen) during postprandial state. NAFLD subjects have increased insulin resistance (IR), especially in the liver (Hep-IR) and are at higher risk of hyperglycemia and type 2 diabetes (T2DM). However, the pathophysiological mechanisms for increased EGP and Hep-IR are still not known. Since both amino-acids and lipids contributes through gluconeogenesis to EGP, the goal was to evaluate if concentrations of glucogenic amino-acids (glutamate, alanine, branched chain amino acids (BCAA), and aromatic amino acids (AAA)) were increased and associated with EGP and Hep-IR in lean (ie without the confounding presence of obesity) non diabetic NAFLD.
Methods: We studied 44 non diabetic NAFLD subjects with liver biopsy (29 non-Obese, NAFLD-NO and 15 Obese NAFLD-Ob) and 20 non-obese controls (CT). We measured fasting EGP (by tracer infusions), plasma amino acid and free fatty acid (FFA) concentrations by GCMS and calculated Hep-IR (EGPxInsulin), HOMA and Adipo-IR (FFAxInsulin). Non-normally distributed variable were ln-transformed.
Results: From CT to NAFLD-NO to NAFLD-Ob we observed the increase in EGP (584±44 to 710±23 to 839±40 umol/min, p<0.0002) and Hep-IR (52±6 to 96±6 to 166±23 umol/kg/min x mU/l, p<0.001). Both EGP and ln(Hep-IR) increased proportionally to ln(ALT) (R=0.47 and R=0.55, p<0.0005), ln(AST) (R=0.39 and R=0.48, p<0.003), and degree of fibrosis (R= 0.55 and R=0.44, p<0.001). EGP correlated positively with ln(BCAA) (R= 0.35, p<0.009), ln (AAA) (R=0.48, p<0.0002), and ln(glutamate) (R=0.29, p<0.03); ln(Hep-IR) with ln (AAA) (R=0.33, p<0.01), and ln(alanine) (R=0.29 p<0.03). Fibrosis score was positively correlated to ln(AAA) (R=0.34, p<0.005), ln(glutamate) (R=0.38, p<0.001), ln(BCAA) (R=0.30, p<0.01), ln(alanine) (R=0.29, p<0.02).
Conclusions: Higher glucogenic amino-acid concentrations observed in NAFLD are positively associated to increased EGP, Hep-IR and fibrosis score and might explain, at least in part, the increased risk of hyperglycemia and T2DM observed in NAFLD.

Disclosure of Interest: None Declared